Claims 2-9 and 28-39 have been rejected under 35 USC 112, first paragraph, because the specification, while being enabling for a method for inhibiting tumor cell proliferation *in vitro*, does not reasonably provide enablement for a method of inhibiting tumor cell proliferation *in vivo*. The examiner states that demonstrating inhibition of cell growth by administration of leptin to cell lines growing *in vitro*, cannot alone support the predictability of the method for treating a tumor growing *in situ* through administration of leptin. The examiner states that it is well known that the art of anti-cancer drug discovery for cancer therapy is highly unpredictable and, thus, no one skilled in the art would accept the assertion that the method comprising the administration of leptin would function as claimed based only upon the known mechanism of action of leptin on cells grown in culture. The examiner further refers to the fact that tumors resist penetration by drugs. The examiner further states that an effective chemotherapeutic must selectively kill tumor cells. The examiner states that the instant formulations of the method are not selective for tumor cells, nor would it be expected that the formulation would act only on dividing tumor cells since the leptin receptor occurs ubiquitously. The examiner states that the specification does not teach how to make/use a formulation with specific targeting, and that the formulation may have an inherently short half-life and otherwise may not reach the target. Thus, the examiner contends that it would take undue experimentation to practice the claimed invention. This rejection is respectfully traversed.

First of all, as to the examiner's comments that one cannot predict *in vivo* results from *in vitro* data, please note the attached abstracts:

> Kiberstis, "Cancer Therapy on Target", Science 292:399-401 (2001);
>
> Druker et al, "Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia", N. Engl. J. Med. 344:1084-6 (2001);
>
> Waller et al, "Growth inhibition of Ph+ progenitor cells from CML patients using the tyrosine kinase inhibitor CGP57148B", Anticancer Res. 20:809-14 (2000);
>
> Buchdunger et al, "Inhibition of the Abl protein-tyrosine kinase in vitro and in vivo by a 2-phenylaminopyrimidine derivative", Cancer Res. 56:100-4 (1996).

These show how an agent (STI571, formally known as CGP57148B) was identified in 1996 as an inhibitor of cell proliferation in culture. This agent was eventually found to be effective in curing chronic myelogenous leukemia and possibly other types of cancer. The most relevant statements in these abstracts are highlighted. Another example is IFN-α which was first found to inhibit cell proliferation *in vitro* back in the sixties and later successfully used clinically in hairy cell leukemia, CML and melanoma. Thus, *in vitro* success cannot automatically be disregarded as evidence of an expectation of usefulness *in vivo*.

Reference is made to MPEP §2107 III. "Therapeutic or Pharmacological Utility". This section quotes with approval, for example, from Cross v. Iizuka, 224 USPQ 739, 747-48 (Fed. Cir.

1985), where it commented on the significance of data from *in vitro* testing which showed pharmacological activity, stating:

> We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, *in vitro* testing, may establish a practical utility for the compound in question. Successful *in vitro* testing will marshal resources and direct the expenditure of effort to further *in vivo* testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vivo* utility.

This section of the MPEP also quotes In re Brana, 34 USPQ2d 1436 (Fed. Cir. 1995) to the effect that Phase II testing is not necessary in order to prove utility. Furthermore, the last paragraph of this section states:

> These general principles are equally applicable to situations where an applicant has claimed a process for treating a human or animal disorder. In such cases, the asserted utility is usually clear - the invention is asserted to be useful in treating the particular disorder. If the asserted utility is credible, there is no basis to challenge such a claim on the basis that it lacks utility under 35 USC 101. [Emphasis original]

Note also Ex parte Bhide, 42 USPQ2d 1441, 1447 (Bd. Pat. App. & Int. 1996), where it states:

> A specification which contains a statement of the manner and process of using the invention in terms which correspond in scope to those used in defining the subject sought to be patented *must* be taken as in compliance with the "how-to-use" requirement

> of the first paragraph of 35 U.S.C. §112 *unless* there is a reason to doubt the objective truth of the statement. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995); *In re Marzocchi*, 439 F.2d 220, 223, 160 USPQ 367, 369 (CCPA 1971). [Emphasis original]

This case further goes on to state at 1447:

> Applicants' statement of utility that cancer may be treated with compounds which inhibit farnesyl protein transferase is not inherently incredible. Whatever might have been the case earlier in the 20th Century, in 1992 when applicants filed their application, the notion that a chemical compound may be useful in treating cancer is not inherently incredible.

Note that the same case further states at 1448:

> The examiner notes that there are no *in vitro* or *in vivo* test results described in the specification. Whether *in vitro* or *in vivo* tests are needed depends on the facts of each case. The examiner did not explain why, in this case, *in vitro* or *in vivo* tests should be required.

Thus, the lack of *in vivo* testing in the present specification is an insufficient basis to conclude that the stated *in vivo* activity would be considered incredible by those skilled in the art.

As to the examiner's assertion that an effective chemotherapeutic must selectively kill tumor cells, it must be understood that the present specification does not contend that leptin selectively kills tumor cells. Leptin is not a cytotoxic agent and does not work in the way that conventional cytotoxic

chemotherapeutics work. The present specification makes clear that the treatment of cancer by means of leptin involves inhibition of tumor cell proliferation by biological means mediated by the leptin receptor which occurs on the tumor cells. Thus, all of the examiner's comments about how tumors resist penetration by drugs, are irrelevant as it is only necessary for the leptin to reach the cell surface receptor on the tumor cells, not to penetrate the tumor cell in order to have its action.

Furthermore, the examiner's comments about the leptin receptor occurring ubiquitously would not be expected to cause a problem as it is well known that leptin may be administered for various purposes without adverse events. Attached hereto are abstracts of the following three publications which confirm this fact:

> Heymsfield et al, "Recombinant leptin for weight loss in obese and lean adults: a randomized, controlled, dose-escalation trial", JAMA 282:1568-75 (1999).
>
> Hukshorn et al, "Weekly subcutaneous pegylated recombinant native human leptin (PEG-OB) administration in obese men.", J. Clin. Endocrinol. Metab., 85:4000-4002 (2000);
>
> Bowles et al, "Leptin: of mice and men?", J. Clin. Pathol. 54:1-3 (2001);

These third-party clinical results for the treatment of humans with leptin show that for normal cells there are no adverse events in the administration of leptin. Thus, it would not be expected that there would be adverse events in the administration of leptin for the purpose of inhibiting tumor cell proliferation.

As to the examiner's comment that variables such as biological stability, half-life, or clearance from the blood are important parameters in achieving successful therapy, reference is made to the attached abstract of Ahren et al, "Pharmacokinetics of human leptin in mice and rhesus monkeys", Int. J. Obes. Relat. Metab. Diord., 24:1579-85 (2000). This abstract shows a very good half-life in rhesus monkeys as well as in mice and further confirms the credibility of the statements made in the present specification.

In conclusion, the present claims are directed to a method for treating tumors in mammals or for inhibiting tumor cell proliferation in mammals. The preferred compound being administered is leptin and the specification discloses that leptin is active in inhibiting tumor cell proliferation in *in vitro* tests on tumor cell lines, and that it is effective due to the binding of the leptin to its receptor on the tumor cells and the activation of that receptor. Inhibition of proliferation of tumor cell lines *in vitro* ~~was found to be an adequate predictor~~ of success *in vivo* in other compounds such as STI571 and IFN-α. Furthermore, leptin has been shown to be safe, without adverse events, when used *in vivo* in humans and other mammals for indications other than cancer, and that it has a reasonable half-life *in vivo*. Since no adverse events have been shown by the general administration of leptin to humans, adverse events would not be expected when leptin is administered for the purpose of the treatment of tumor cells in order to inhibit their proliferation. Again, the present claims do not require that the tumor cells be

no correlation

killed or that the tumors enter remission, but only that the tumor cell proliferation be inhibited or that the tumor be treated, i.e., that the tumor condition be ameliorated such as, for example, by inhibition of proliferation of the tumor cells. Thus, in light of all of this evidence, it is not incredible that leptin will be useful *in vivo* in mammals. *In vivo* proof should not be necessary in view of the convincing *in vitro* results and the post-filing date publications which serve to confirm the statements of utility made in the present specification.

For all of these reasons, reconsideration and withdrawal of this rejection are respectfully urged.

Claims 2-9 and 28-39 have been rejected under 35 USC 112, first paragraph, because the specification, while being enabling for leptin and leptin fusion proteins, does not reasonably provide enablement for leptin muteins, leptin receptor agonists, active fragments or fractions thereof, active analogs or derivatives of any thereof, and mixtures of any thereof as inhibitors of tumor cell proliferation. This rejection is respectfully traversed.

First of all, it is not understood why the examiner includes claims 9, 29 or 35 in this rejection, as the examiner has conceded that the specification is enabling for these species. Accordingly, reconsideration and withdrawal of this rejection at least with respect to these claims are respectfully urged.

The examiner objects to the definition of leptin muteins as being proteins having at least 60%, 70%, 80% or 90% identity with the sequence of leptin. It is noted that claim 28 is

directed to 60% identity; claim 37 specifies 70% identity; claim 38 specifies 80% identity; and claim 39 specifies 90% identity. The examiner treats all of these claims the same. The examiner states that the specification has not demonstrated that leptin variants are capable of functioning as that which is suggested. The examiner states that these definitions, including the definition of a sequence encoded by a nucleic acid which hybridizes to a nucleic acid which encodes leptin under stringent conditions and has the ability to block cell proliferation do not define the sequence of the variant product. The examiner states that in view of the unpredictable nature of protein chemistry, this is never acceptable. This part of the rejection is respectfully traversed.

The examiner's attention is respectfully drawn to the Revised Interim Written Description Guidelines Training Materials and, particularly, Example 14: "Product-by-Function". In that example, the specification exemplified a protein isolated from liver that catalyzed the reaction of A→B, which isolated protein was sequenced and was determined to have the sequence as set forth in SEQ ID NO:3. The specification also contemplated, but did not exemplify, variants of the protein wherein the variant can have any or all of the following: substitutions, deletions, insertions, and additions. The specification indicated that procedures for making proteins with substitutions, deletions, insertions, and additions is routine in the art and provides an assay for detecting the catalytic activity of the protein.

This description in the specification is very similar to the description which appears in the present specification. The present specification exemplifies a protein that inhibits tumor cell proliferation *in vitro*. The sequence of this protein is known. The specification contemplates, but does not exemplify, variants of the protein wherein the variant can have substitutions, deletions, insertions, and additions. The present specification also indicates that procedures for making proteins with substitutions, deletions, insertions, and additions is routine in the art and provides an assay for determining whether any given protein inhibits tumor cell proliferation.

In Example 14 of the Training Materials, the claim is directed to:

> A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A→B.

The present claim 39 is drawn to a method of use that includes a mutein of leptin having at least 90% identity with the sequence of a leptin and has the ability to block cell proliferation. Thus, this claim is very similar to that of Example 14.

The analysis in the Training Materials acknowledges that procedures for making variants of SEQ ID NO:3 are conventional in the art and that an assay is described which will identify other proteins having the claimed functionality. Moreover, procedures for making variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity were conceded as being conventional in the art. It would, of course, be understood that

procedures for making variants of leptin which have 90% identity to the sequence of leptin and retain its activity are also conventional in the art, as are procedures for making variants which have 80%, 70%, and 60% identity.

The analysis goes on to point out that all variants of the claim must possess the specified catalytic activity and must have at least 95% identity to the SEQ ID NO:3. Furthermore, because of the "comprises" language, the protein claimed may be larger than SEQ ID NO:3 or its variant with 95% identity to SEQ ID NO:3. The analysis points out that the specification contains a reduction to practice of the single disclosed species. The analysis concludes:

> The specification indicates that the genus of proteins that must be variants of SEQ ID NO:3 does not have substantial variations since all the variants must possess the specified catalytic activity and must have at least 95% identity to the reference sequence, SEQ ID NO:3. The single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus.
>
> **Conclusion:** The disclosure meets the requirements of 35 USC §112, first paragraph, as providing adequate written description for the claimed invention.

Thus, it is apparent that if the single species disclosed is representative of the genus and an assay is present for identifying the members of the variants which are capable of the specified functionality, the written description requirement is met regardless of the protein chemistry arguments made by the examiner. The difference between 95% in the training materials and 90% in claim 39 is not great enough to distinguish claim 39 and cause the analysis to come out in a different manner than in Example 14 of the training materials. The same is true for the 80% of claim 38, 70% of claim 37, and 60% of claim 28.

Furthermore, the examiner's comments about what effect a single amino acid change might have, does not really represent the state of the art. It is much more common that random changes will have no effect on the properties of the protein. Certainly, conservative changes would be expected to be tolerated. Furthermore, many portions of a long protein have nothing whatsoever to do with the specific activity being claimed and, therefore, it would not be expected that changes in these portions would affect the functionality. It is unduly limiting to require an applicant to claim only the exemplified embodiments. Note In re Goffe, 191 USPQ 429, 431 (CCPA 1976), where it states:

> For all practical purposes, the board would limit appellant to claims involving the specific materials disclosed in the examples, so that a competitor seeking to avoid infringing the claims would merely have to follow the disclosure in the subsequently issued patent to find a substitute. However, to provide effective incentives, claims must adequately protect inventors. To demand that the first to

> disclose shall limit his claim to what he has found will work or to materials which meet the guidelines specified to "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts. See In re Fuetterer, 50 CCPA 1453, 1462, 319 F.2d 259, 265, 138 USPQ 217, 223 (1963)

It would not require undue experimentation to test any given mutein to determine if it retains the properties of inhibiting tumor cell proliferation. 90% identity is a reasonable correlation between the scope of the claims and the scope of enablement. 80%, 70%, or even 60% is also reasonable in light of the functionality assay disclosed in the specification.

It should be noted that it is extremely common in patents directed to proteins to grant some degree of breadth so that a patentee is not limited to the specific protein which he has discovered will work. Attached hereto are the front page and claims of 15 patents that have such language encompassing varying degrees of identity. It is believed that hundreds of such patents exist. Has the Patent and Trademark Office changed its position since the issuance of those patents so as to refuse to grant claims to muteins because there is some amount of unpredictability about amino acid replacement?

For all of the reasons discussed herein, reconsideration and withdrawal of this part of the rejection are respectfully urged.

The examiner also objects to the "fragment" language. The examiner states that this language reads on small fragments. The examiner further states that since there is no enablement for

a mutein, there is no enablement for a fragment of a mutein. The examiner states that it would not be expected that all fragments would work in view of the folded three-dimensional structure of proteins, and, therefore, it would involve undue experimentation to practice the invention as claimed. This part of the rejection is also respectfully traversed.

Applicant is not taking the position that small fragments will necessarily work. However, it would be expected that if one amino acid were removed from the C-terminus that the fragment which remains will still be active. It is within the skill of the art to remove one amino acid at a time from either end of a protein or a mutein, and then run the assay to determine if the fragment retains functionality. Once a fragment loses functionality, then it is not necessary to test any further. This does not involve undue experimentation. One of ordinary skill in the art would not start picking random fragments and run them through the assay. Those of ordinary skill in the art would use a procedure such as discussed above, or some other such rational procedure. This would not involve undue experimentation. As stated at MPEP §2164.06, a considerable amount of experimentation is permissible if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Reconsideration and withdrawal of this part of the rejection are also respectfully urged.

With respect to the hybridization language, reference is made to Example 10: "Process Claim" in the training materials. This example concludes:

> Now turning to the genus analysis, the art indicates that there is no substantial variation within the genus because of the stringency of hybridization conditions which yields structurally similar molecules. The single disclosed species is representative of the genus because reduction to practice of this species, considered along with the defined hybridization conditions and the level of skill and knowledge in the art, are sufficient to allow the skilled artisan to recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus.

Therefore, it is clear that there is no written description problem with this hybridization language. Because stringent conditions are specified, it would not involve undue experimentation to test whatever is found, after such stringent condition hybridization, in the tumor cell proliferation assay described in the specification. Accordingly, this language as well fully complies with the first paragraph of 35 USC 112. Reconsideration and withdrawal of this rejection insofar as it relates to the hybridization language are therefore also respectfully urged.

For all of these reasons, reconsideration and withdrawal of this entire rejection are respectfully urged.